APPENDIX A

"Version with markings to show changes made"

In the specification:

Please replace the priority information at the top of page 1 specification with the following paragraph,

This application is a Continued-Prosecution-Application and claims [P]priority under 35 U.S.C. §120 to [of] Continued-In-Part U.S. application Serial No. 09/374,554, filed August 13, 1999, and Continued-In-Part U.S. application Serial No. 09/322,864, filed on May 28, 1999. [, and U.S. application Serial No. 09/233,611, filed on January 19, 1999 is claimed under 35 U.S.C. 120. Priority of U.S. application Serial No. 60/079,399, filed March 26, 1998, and U.S. application Serial No. 60/071,940, filed January 20, 1998, and U.S. application Serial No. 60/105,968, filed October 28, 1998, is claimed under 35 U.S.C. 119.] The contents of each of the aforementioned applications are expressly incorporated by reference.

Please replace page 1, line 35 through page 2, line 9 of the specification with the following paragraph,

In the realm of cancer therapy it often happens that a therapeutic agent that is initially effective for a given patient becomes, overtime, ineffective or less effective for that patient. The very same therapeutic agent may continue to be effective over a long period of time for a different patient. Further, a therapeutic agent that is effective, at least initially, for some patients can be completely ineffective or even harmful for other patients. Accordingly, it would be useful to identify genes and/or gene products that represent prognostic markers with respect to a given therapeutic agent or class of therapeutic agents. It then may be possible to determine which patients will benefit from particular therapeutic regimen and, importantly, determine when, if ever, the therapeutic regime begins to lose its effectiveness for a given patient. The ability to make such predictions would make it possible to discontinue a therapeutic regime that has lost its effectiveness well before its loss of effectiveness becomes apparent by conventional measures.

Please replace page 35, lines 9-18 of the specification with the following paragraph,

Activity database (A)

Two tables were created: a table consisting of the growth inhibition (GI_{50}) values for 54 of the 60 cell lines and 171 compounds was created from the NCI-DTP *in vitro* cancer screen database. These were the seed compounds representing the major classes of compounds present in the larger 23,000 compounds database available from the DTP. The seed compounds were selected on the basis of their known mechanism of action and chemical structure. The average potency -log{GI_{50}} was extracted from the flat comma-delimited text files. [available through the Web at http://www.nci.nih.gov/intra/lmp/jnwbio.html.] Missing values were left as a blanks in the data tables.

Please replace page 36, lines 1-8 of the specification with the following paragraph,

The isolated polyA RNA (2 μg) was used to synthesize cDNA using Gibco BRL Superscript Choice System cDNA Synthesis Kit. The following modified T7 RNA polymerase promoter -[T]24 primer was used:

5'-GGCCAGTGAATTGTAATACGACTCACTATAGGGAGGCGG-[T]24-3' (SEQ ID NO:1)

Please replace page 45, lines 6-27 of the specification with the following two paragraphs,

In the second study, nucleic acid arrays were used to determine the level of expression of approximately 6500 nucleic acid sequences in a relatively TAXOL resistant human mammary epithelial cell primary cell line (HMEC) and in a relatively TAXOL sensitive breast cancer cell line (MDA-435) in the presence of TAXOL. This analysis led to the identification of genes that are relatively highly expressed in the TAXOL resistant human mammary epithelial cell primary cell line compared to the relatively TAXOL sensitive breast cancer cell line (Table 10A) and genes that are relatively highly expressed in the relatively TAXOL sensitive breast cancer cell line compared to the relatively TAXOL resistant human mammary epithelial cell primary cell line (Table 10B).

In the third study, nucleic acid arrays were used to determine the level of expression of [approximately ____] nucleic acid sequences in [breast] ovarian cancer clinical samples obtained from patients whose [breast] ovarian cancer appeared to respond to TAXOL/cisplatin combination therapy over an initial six month treatment period ("TAXOL/cisplatin sensitive clinical samples") and [breast] ovarian cancer clinical samples obtained from patients whose [breast] ovarian cancer appeared to respond poorly to TAXOL/cisplatin combined therapy over and initial six month treatment period ("TAXOL/cisplatin resistant clinical samples"). This analysis led to the identification of genes that are expressed at a relatively high level in the TAXOL/cisplatin resistant clinical samples compared to the TAXOL/cisplatin sensitive clinical samples (Table 11A) and genes that are expressed at a relatively low level in the TAXOL/cisplatin resistant clinical samples compared to the TAXOL/cisplatin sensitive clinical samples (Table 11B).

Please replace page 46, lines 6-13 of the specification with the following paragraph,

The Affymetrix HUM6000 GeneChip system (Santa Clara, CA) was used to measure expression of approximately 6500 nucleic acid sequences in the selected cell lines. The cRNA used for expression analysis was prepared as follows. First, double passed polyA RNA was prepared from the cell line pellets (~10^8 cells/pellet) using Invitrogen Fast Track 2.0 system. Next, cDNA was prepared from 2μg of polyA RNA using Gibco BRL Superscript Choice System cDNA Synthesis Kit. The following modified T7 RNA polymerase promoter -[T]24 primer was used:

5'- GGCCAGTGAATTGTAATACGACTCACTATAGGGAGGCGG-[T]24-3' (SEQ ID NO:2)

Please replace page 50, lines 22-25 of the specification with the following paragraph,

The clinical samples were obtained from patients undergoing [breast] ovarian cancer therapy at the Mayo Clinic (Rochester, MN). Gene expression was measured as described above for the first study of TAXOL resistant and TAXOL sensitive cell lines except that a proprietary nucleic acid array was used to measure expression.

In the claims:

Please amend claims 3, 6, 12, 18, 21, 27, 32, 33, 35 and 36 as follows:

3. **(Amended)** A method for determining whether TAXOL cannot be used to reduce the growth of breast cancer cells, comprising the steps of:

a) obtaining a sample of breast cancer cells;

b) determining whether said breast cancer cells express [one or more genes selected from the group consisting of the resistance genes identified in Tables 8A, 9A, 9B, 9C, 9D, 10A, and 11A] the BST-2 gene; and

c) identifying that TAXOL cannot be used to reduce the growth of said breast cancer cells when [one or more of said genes] said BST-2 gene is expressed by said breast cancer cells.

6. **(Amended)** The method of claim 3, wherein said level of expression is determined by detecting the amount of mRNA that is encoded by said [one or more genes] BST-2 gene present in said sample.

12. **(Amended)** The method of claim 3, wherein said breast cancer cells are selected from the group consisting of breast cancer cell lines and breast cancer cells obtained from a patient.

18. **(Amended)** A method for determining whether TAXOL cannot be used to reduce the growth of breast cancer cells, comprising the steps of:

a) obtaining a sample of breast cancer cells;

b) exposing the breast cancer cells to TAXOL;

c) determining the level of expression in the breast cancer cells of [one or more genes selected from the group consisting of the resistance genes identified in Tables 8A, 9A, 9B, 9C, 9D, 10A, and 11A] the BST-2 gene in the sample exposed to the TAXOL and in a sample of breast cancer cells that is not exposed to TAXOL; and

d) identifying that TAXOL cannot be used to reduce the growth of said breast cancer cells when the expression of [one or more of said genes] said BST-2 gene is increased in the presence of TAXOL.

21. **(Amended)** The method of claim 18, wherein said level of expression is determined by detecting the amount of mRNA that is encoded by said [one or more genes] BST-2 gene present in said sample.

27. **(Amended)** The method of claim 18, wherein said breast cancer cells are selected from the group consisting of breast cancer cell lines and breast cancer cells obtained from a patient.

32. **(Amended)** A method for determining whether treatment with TAXOL should be continued in a breast cancer patient, comprising the steps of:

a) obtaining two or more samples comprising breast cancer cells from a patient during the course of TAXOL treatment;

b) determining the level of expression in the breast cancer cells of [one or more genes selected from the group consisting of the resistance genes identified in Tables 8A, 9A, 9B, 9C, 9D, 10A, and 11A] the BST-2 gene in the two or more samples; and

c) discontinuing treatment when the expression level of [one or more of said genes] said BST-2 gene increases during the course of treatment.

33. **(Amended)** A method for determining whether treatment with [a] TAXOL should be continued in a breast cancer patient, comprising the steps of:

a) obtaining two or more samples comprising breast cancer cells from a patient during the course of TAXOL treatment;

b) determining the level of expression in the breast cancer cells of [one or more genes selected from the group consisting of the resistance genes identified in Tables 8A, 9A, 9B, 9C, 9D, 10A, and 11A] the BST-2 gene in the two or more samples; and

c) continuing treatment when the expression level of [one or more of said genes] said BST-2 gene does not increase during the course of treatment.

35. **(Amended)** The method of claim 32, wherein said level of expression is determined by detecting the amount of mRNA that is encoded by said [one or more genes] BST-2 gene present in said sample.

36. **(Amended)** The method of claim 33, wherein said level of expression is determined by detecting the amount of mRNA that is encoded by said [one or more genes] BST-2 gene present in said sample.